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RISK ASSESSMENT FOR THE IMPURITIES 2-BUTOXYETHANOL AND 1,4-DIOXANE FOUND IN GARLON 4 AND ROUNDUP HERBICIDE FORMULATIONS

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ABSTRACT

The risk assessment for the impurities 2-butoxyethanol and 1,4-dioxane found in Garlon 4 and Roundup herbicide formulations, respectively, shows that the addition of these impurities does not substantially increase the risk to human health or to fish and wildlife resources over the risk identified in the Region 5 FEIS for the active ingredients triclopyr and glyphosate.

HUMAN HEALTH RISKS

INTRODUCTION

Concern about the possible toxic properties of inert ingredients and full herbicide formulations was expressed during public involvement for both site specific project analyses and the Region 5 Vegetation Management for Reforestation Final Environmental Impact Statement (FEIS). The issue of inert ingredients and the toxicity of formulations is discussed in the FEIS (pages 4-116 through 4-119).

The U.S. Environmental Protection Agency has categorized approximately 1200 inert ingredients into four lists. Lists 1 and 2 contain inert ingredients of toxicological concern (FEIS, 4-416; Fed. Reg. 54:48314-16). Since most information about inert ingredients is classified as "Confidential Business Information" the Forest Service relied on EPA to review the formulations and tell us whether they contained inert ingredients of toxicological concern (FEIS, 4-117). We have also received information from the companies which produce the herbicides and spray additives.

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The chemical companies and the EPA have identified three compounds that are included on inert ingredient list 1 or 2; kerosene and 2-butoxyethanol in ester formulations of triclopyr, and 1,4-dioxane in the surfactant used in the Roundup formulation of glyphosate (FEIS 4-117, Monsanto 1990, and Dow Chemical USA 1988). Kerosene is used as an inert ingredient in the formulation of triclopyr ester formulated products while 2-butoxyethanol is an impurity in the active ingredient triclopyr ester. 1,4-dioxane is an impurity in the surfactant used in formulating glyphosate as the formulated product Roundup.

The EPA defines the term impurity as "... any substance in a pesticide product other than an active ingredient or an intentionally-added inert ingredient; the term includes beginning materials, side-reaction products, contaminants, and degradation products" (40 CFR 158.108(3).

Current Forest Service policy is to permit use of formulations containing inert ingredients on EPA List 3 and 4. Formulations containing List 1 or 2 chemicals are used only when no formulation with only List 3 or List 4 inert ingredients is available to meet project objectives, and only after an evaluation of the inert ingredient shows that health risks are acceptable. A risk analysis for kerosene was completed for the FEIS (page F-77). The following assessment examines the human health, fish and wildlife risks associated with herbicide formulations containing the impurities 2-butoxyethanol and 1,4-dioxane.

To analyze human health risks of these two impurities, we followed the same procedures used in the FEIS (Appendix F) in assessing the risks of the herbicide active ingredients. These procedures involve comparing estimated doses of the ingredients with toxicity levels found in laboratory animals.

Estimated doses of these impurities were calculated by multiplying herbicide doses (Table F-28, F-29, F-32 and F-33, pages F-94 through F-99, FEIS) by correction factors for the concentration of the impurity in the formulation and for the dermal absorption rate of the impurity using the following equation:

ID = HD X ICF X DPCF

where:

ID	=	Impurity dose
HD	=	Herbicide dose (Tables F-28, F-29, F-32 and F-33)
ICF	=	Impurity correction factor based on the ratio of impurity to active ingredient in the herbicide formulation.
DPCF	=	Dermal penetration correction factor derived from the ratio of the dermal penetration rate of the impurity to the dermal penetration of the herbicide.

Dose values for triclopyr were first corrected for a dermal absorption rate of 1.65 percent based on data submitted by Dow Chemical Company rather than the 6 percent used in the FEIS (Carmichael et al. 1989). Doses for mechanical ground applications of herbicides were obtained from Tables 4-31 and 4-40 (pages 4-75 and 4-84) in the Region 8 FEIS for Vegetation Management in the Coastal Plain/Piedmont (1989).

The average concentration of the impurity 2-butoxyethanol in Garlon 4 herbicide formulation is 0.3% (Dow Chemical Company 1990c) and the dermal penetration rate used is 6.9% (Bartnik et al. 1987). The average concentration of 1,4-dioxane in the Roundup formulation is 0.03% and the dermal penetration rate used is 10% (Heydens 1990).

Therefore, the dose of 2-butoxyethanol is:

$$ID = HD \times 0.3\%/44.3\% \times 6.9\%/1.65\% = 0.028HD$$

and of 1,4-dioxane:

$$ID = HD \times 0.03/30.4\% \times 10\%/6\% = 0.0016HD$$

The results of the dose calculations are presented in Tables 1 and 2.

The literature was examined to identify major health effects and toxicity data. NOEL values for the common routes of exposure were identified for systemic and reproductive effects and the lowest NOEL values (Table 3) were used with various doses to workers and the public to calculate Margins of Safety (see Tables 4 through 18).

2-BUTOXYETHANOL

2-butoxyethanol (ethylene glycol monobutyl ether or EGBE) is a major industrial chemical used in a wide range of industrial and commercial applications such as surface coatings and cleaners, chemical intermediates, and a general solvent in various household cleaning agents and aerosols (Bartnik et al. 1987, Ghanayem 1989, Ghanayem et al. 1987b, Grant et al. 1985, Krasavage 1986). Ghanayen et al. (1987a) indicated that over 742 consumer products contain EGBE at an average concentration of 2.8%.

EGBE has been identified as a manufacturing impurity of the triclopyr ester used in the Garlon 4 formulation. It is not an intentionally added inert ingredient. Testing indicates EGBE is present in Garlon 4 at an average concentration of less than 0.3% (Dow Chemical Company 1990c).

Using an acute oral LD_{50} for rats of 470 mg/kg (Dow Chemical Company 1990a), EGBE is classified as a moderately toxic compound (EPA Category II). It is also moderately toxic for dermal exposures (LD_{50} for rabbits of 220 mg/kg). EGBE presents a slight to moderate acute hazard to humans from single exposure by skin contact or by swallowing (Tyler 1984). Based on the calculated environmental doses (Table 1 and 2) resulting from herbicide applications, EGBE in triclopyr formulations presents little or no acute hazard to humans.

The primary toxic effect of EGBE is to make the red blood cells more fragile which can result in decreased hemoglobin concentration, red blood cell counts, and mean corpuscular hemoglobin concentration. These blood effects have been seen primarily in rodents and to a lesser degree in other laboratory animals. In vitro studies suggest that humans of both sexes are not as susceptible as rodents to these blood effects (Bartnik et al. 1987, Ghanayem et al. 1989).

Secondary effects of EGBE include increased liver, kidney, and spleen weights and reduced thymic weight. Tyler (1984) and Dow Chemical Company (1990b) cite an unpublished study that reported EGBE induced testicular atrophy at oral doses of 200 mg/kg/day. However, the EGBE used in the study contained impurities of crown ethers which are known to cause testicular atrophy. These data are considered suspect and are not supported by later studies. Testicular effects have not resulted from other oral, dermal, or inhalation exposures to EGBE (Grant et al. 1985, Krasavage 1986, Tyler 1984).

In his review of EGBE acute and subchronic toxicity studies, Tyler (1984) reported systemic NOELs for oral (80 mg/kg), dermal (150 mg/kg), and inhalation (25 ppm) exposures. Bartnik et al. (1987) concluded that the potential for toxic uptake of EGBE is more likely due to excessive skin exposure than vapor inhalation. Our calculations of inhalation exposures of EGBE from forestry applications of triclopyr also indicate extremely low doses (1.7×10^{-7} mg/kg) even for worst case estimates. Using modeling for rats (Lasiewski and Calder 1971, Sparer et al. 1988, USDA Forest Service 1989) the systemic inhalation NOEL was determined to be about 19.8 mg/kg. Even though inhalation is the most unlikely route of exposure from herbicide applications, this systemic NOEL is used because it is the lowest NOEL found in the literature. Comparisons of the environmental dose data (Table 1 and 2) with this systemic NOEL give MOS values of 3000 or greater even for worst case exposure conditions (Tables 4 through 18).

Reproductive studies with rats have found increased embryo- and feto- toxicity associated with doses that cause maternal toxicity, but no evidence of teratogenicity (Dow Chemical Company 1990b, Hardin et al. 1984, Tyl et al. 1984, Wier et al. 1987). For example, Wier et al. (1987) dosed mated, female rats by oral gavage and found embryo lethality (increases in embryo resorption) was associated with maternally toxic doses of 1,000 mg/kg/day or greater (NOEL = 650 mg/kg/day). Maternal toxicity (death, morbidity, and distinctive staining of cage papers) was observed at doses of 650 mg/kg/day or greater (NOEL = 350 mg/kg/day). There were no differences in numbers of implants, dead or live fetuses, malformed fetuses, or in fetal weights. There also was no evidence of developmental toxicity as measured by differences in survival or body weight of young born to females dosed at maternally toxic levels. Hardin et al. (1984) reported no embryotoxic, fetotoxic, or teratogenic effects from a dose of 0.12 mL (2,400 mg/kg/day) applied to the shaved skin of rats even though EGBE readily penetrates the skin. Tyl et al. (1984) found that inhalation exposures of 100 ppm or greater resulted in maternal toxicity and caused embryo toxicity and fetotoxicity, but no fetal malformations. They found no maternal, embryo, or fetal toxicity (including malformations) at 50 ppm (NOEL = 39.6 mg/kg/day). While oral and dermal uptake are more likely routes of exposure to EGBE from herbicide applications, we have used the lower inhalation NOEL of 39.6 mg/kg/day in our assessment of human reproductive risks (Table 3). Comparisons of the environmental dose data (Table 1 and 2) with this reproductive NOEL give MOS values of 5,800 or greater even for worst case exposure conditions (Tables 4 through 18). The health effects data indicate that EGBE does not represent a reproductive hazard to men or women (Dow Chemical Company 1990a, 1990b).

1,4-DIOXANE

1,4-dioxane (dioxane) is a common solvent used in laboratories and industrial applications. This chemical is also a trace impurity of many (over 35,000) household, personal-use products such as detergents, soaps, shampoos, and cosmetics; and it also is found in polysorbates approved for use in processed foods (Fishbein 1981, Monsanto 1990).

Dioxane is a manufacturing impurity in the ethoxylated surfactant used in Roundup, a formulation of glyphosate. It is not an intentionally added ingredient. Testing indicates that a reasonable estimate of the upper-limit concentration of dioxane in the herbicide formulation is 0.03%.

Using the acute oral LD_{50} of 4,200 mg/kg (Layton et al. 1987, Lewis and Sweet 1984), dioxane is classified as a slightly toxic compound (EPA Category III). The principal toxic effects of dioxane are damage to the liver and kidneys in humans and test animals (Fishbein 1981, Hartung 1989, Kociba et al. 1974, Torkelson et al. 1974, Young et al. 1978). These effects have been seen in both acute and chronic exposures to high doses (Kociba et al. 1974). Based on the calculated environmental doses (Table 1 and 2) resulting from forestry use, dioxane in Roundup presents little or no acute hazard to humans.

High, daily oral doses (>1,000 mg/kg) of dioxane over the lifespan (2 years) of rats caused pronounced toxic effects including the occurrence of liver and nasal tumors (Kociba et al. 1974). In addition to liver and kidney damage, decreases in body weight gains, survival rates, and water consumption were observed. Male and female rats receiving doses of 94 and 148 mg/kg/day, respectively, had liver and kidney damage but no tumors. No evidence of any toxic effects or tumor formation were seen in male and female rats that received an average daily intake of 9.6 and 19 mg/kg/day, respectively, over an entire lifespan. The lower value of 9.6 mg/kg/day reported by Kociba et al. (1974) and Hartung (1989) was used as the systemic NOEL in this analysis (Table 3). Comparisons of the environmental dose data (Table 1 and 2) with this systemic NOEL give MOS values of 10,000 or greater even for worst case conditions (Tables 4 through 18).

In a reproductive study using rats, Giavini et al. (1985) found no effect of dioxane on implanatation numbers, live fetuses, postimplantation loss, or malformations of fetuses. Slight maternal toxicity, expressed as reduced weight gain, was observed at the highest dose (1,034 mg/kg) only, and embryo toxicity, manifested by reduced fetal weight, was ascribed to this maternal toxicity. The authors concluded that dioxane at the doses used was not teratogenic. They give a reproductive NOEL of 516.8 mg/kg/day based on no reproductive effects observed for doses of 0.5 ml/kg (Table 3). Comparisons of the environmental dose data (Tables 1 and 2) with this reproductive NOEL give MOS values of 540,000 or greater for workers and the public even for worst case exposure conditions (Tables 4 through 18).

Dioxane has been established to be a carcinogen at very high doses in test animals. There is no evidence that dioxane is a mutagen or an initatior of cancer (Hartung 1990). Limited human epidemiology studies have shown no association between dioxane and cancer in individuals receiving occupational exposures (Monsanto 1990). Heydens (1990) assessed the cancer risk for

forestry applications of herbicide surfactant containing dioxane. This risk assessment has been reviewed and found to follow the same procedures used in our FEIS (page F-141) and is included as our assessment of the cancer risk from exposures to dioxane in herbicide formulations (Appendix). We agree with Heydens conclusion that the analysis indicates that the carcinogenic risk from exposure to 1,4-dioxane in glyphosate herbicide formulations is negligible for occupationally exposed individuals. The carcinogenic risk to the general public is even less.

TABLE 1

IMPURITY INC NT (mg/kg/day) DOSE ESTIMATES

BASED ON HERBICIDE AC , INGREDIENT APPLICATION RATE PER ACRE

(Aerial Application)

EXPOSURE CLASSES	2-BUTOXYETHANOL			1,4 DIOXANE		
	1.5 lbs.	2.0 lbs.	8.0 lbs.	1.5 lbs.	2.0 lbs.	5.0 lbs.
Workers						
Pilots	8.4×10^{-5}	1.1×10^{-4}	5.0×10^{-3}	1.8×10^{-5}	2.2×10^{-5}	6.4×10^{-4}
Mechanics	2.5×10^{-5}	3.4×10^{-5}	5.9×10^{-4}	5.1×10^{-6}	6.7×10^{-6}	7.6×10^{-5}
Batchmen	9.8×10^{-5}	1.3×10^{-4}	1.8×10^{-3}	2.1×10^{-5}	2.7×10^{-5}	2.4×10^{-4}
Supervisors	7.0×10^{-6}	9.5×10^{-6}	1.1×10^{-4}	1.4×10^{-6}	1.9×10^{-6}	1.5×10^{-5}
Observers	1.8×10^{-6}	2.4×10^{-6}	5.3×10^{-5}	3.5×10^{-7}	4.8×10^{-7}	6.7×10^{-6}
General Public						
Outside Spray Area	3.9×10^{-5}	5.3×10^{-5}	2.6×10^{-4}	8.2×10^{-6}	1.1×10^{-5}	3.3×10^{-5}
Spray	1.8×10^{-8}	2.4×10^{-8}	5.3×10^{-7}	3.5×10^{-9}	4.8×10^{-9}	6.7×10^{-8}
Dietary	3.9×10^{-5}	5.3×10^{-5}	2.6×10^{-4}	8.2×10^{-6}	1.1×10^{-5}	3.3×10^{-5}
Inside Spray Area	4.1×10^{-5}	5.5×10^{-5}	3.1×10^{-4}	8.6×10^{-6}	1.1×10^{-5}	4.0×10^{-5}
Spray	1.8×10^{-6}	2.4×10^{-6}	5.3×10^{-5}	3.5×10^{-7}	4.8×10^{-7}	6.7×10^{-6}
Dietary	3.9×10^{-5}	5.3×10^{-5}	2.6×10^{-4}	8.2×10^{-6}	1.1×10^{-5}	3.3×10^{-5}
Forest Users	5.6×10^{-5}	7.5×10^{-5}	3.7×10^{-4}	1.2×10^{-5}	1.6×10^{-5}	4.7×10^{-5}
Firewood						
Inhalation	2.7×10^{-8}	3.6×10^{-8}	1.7×10^{-7}	5.4×10^{-9}	7.4×10^{-9}	2.2×10^{-8}
Gathers	1.7×10^{-5}	2.2×10^{-5}	1.1×10^{-4}	3.4×10^{-6}	4.5×10^{-6}	1.4×10^{-5}
Dietary	3.9×10^{-5}	5.3×10^{-5}	2.6×10^{-4}	8.2×10^{-6}	1.1×10^{-5}	3.3×10^{-5}
Total Dose to M.E.I.	5.9×10^{-5}	7.8×10^{-5}	4.2×10^{-4}	1.2×10^{-5}	1.6×10^{-5}	5.3×10^{-5}

TABLE 2
IMPURITY INGREDIENT (mg/kg/day) DOSE ESTIMATES
BASED ON HERBICIDE ACTIVE INGREDIENT APPLICATION RATE PER ACRE
(Ground Application)

EXPOSURE CLASSES	2-BUTOXYETHANOL			1,4 DIOXANE		
	1.5 lbs.	2.0 lbs.	8.0 lbs.	1.5 lbs.	2.0 lbs.	5.0 lbs.
Workers						
Backpack	3.4×10^{-4}	4.5×10^{-4}	4.5×10^{-3}	7.0×10^{-5}	9.3×10^{-5}	5.7×10^{-4}
Mechanical						
Applicator	3.1×10^{-5}	4.2×10^{-5}	6.7×10^{-3}	6.6×10^{-6}	8.7×10^{-6}	9.4×10^{-4}
Mixer/Loader	7.4×10^{-5}	9.9×10^{-5}	6.8×10^{-3}	1.6×10^{-5}	2.1×10^{-5}	9.5×10^{-4}
App/Mix/Loader	7.4×10^{-5}	9.6×10^{-5}	9.4×10^{-3}	1.5×10^{-5}	2.1×10^{-5}	1.3×10^{-3}
General Public						
Inside Spray Areas	6.1×10^{-5}	8.2×10^{-5}	4.4×10^{-4}	1.2×10^{-5}	1.6×10^{-5}	5.6×10^{-5}
Spray	1.8×10^{-6}	2.4×10^{-6}	5.3×10^{-5}	3.5×10^{-7}	4.8×10^{-7}	6.7×10^{-6}
Dietary	5.9×10^{-5}	8.0×10^{-5}	3.9×10^{-4}	1.2×10^{-5}	1.6×10^{-5}	4.9×10^{-5}
Forest Users	7.6×10^{-5}	1.0×10^{-4}	5.0×10^{-4}	1.5×10^{-5}	2.1×10^{-5}	6.3×10^{-5}
Firewood						
Inhalation	2.8×10^{-8}	3.6×10^{-8}	1.7×10^{-7}	5.4×10^{-9}	7.4×10^{-9}	2.2×10^{-8}
Gathers	1.7×10^{-5}	2.2×10^{-5}	1.1×10^{-4}	3.4×10^{-6}	4.5×10^{-6}	1.4×10^{-5}
Dietary	5.9×10^{-5}	8.0×10^{-5}	3.9×10^{-4}	1.2×10^{-5}	1.6×10^{-5}	4.9×10^{-5}
Total Dose to M.E.I.	7.8×10^{-5}	1.0×10^{-4}	5.6×10^{-4}	1.6×10^{-5}	2.1×10^{-5}	7.0×10^{-5}

Table 3
Toxicity and Cancer Potency of Impurities
(mg/kg/day)

Impurity	Rat LD_{50}	Dermal LD_{50}	Systemic NOEL	Reprod. Teratogenic NOEL	Cancer Potency
2-butoxyethanol	470	220	19.8	39.6	*
1,4 dioxane	4200	-	9.6	516.8	0.0076

* Cancer potency was not determined for 2-butoxyethanol, since this compound is not a carcinogen.

TABLE 4
MARGINS OF SAFETY FOR EXPOSURE TO THE PUBLIC BY AERIAL APPLICATION:
DERMAL DOSES FROM SPRAY DRIFT

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	1.1×10^{9}	2.2×10^{9}
	2.0 lb.	8.2×10^{8}	1.6×10^{9}
	8.0 lb.	3.7×10^{7}	7.5×10^{7}
1,4-dioxane	1.5 lb.	2.7×10^{9}	1.5×10^{11}
	2.0 lb.	2.0×10^{9}	1.1×10^{11}
	5.0 lb.	1.4×10^{8}	7.7×10^{9}

TABLE 5
MARGINS OF SAFETY FOR EXPOSURE TO THE AERIAL APPLICATION:
CUMMULATIVE EXPOSURE (DRIFT + DIETARY)

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	5.1×10^{5}	1.0×10^{6}
	2.0 lb.	3.7×10^{5}	7.5×10^{5}
	8.0 lb.	7.6×10^{4}	1.5×10^{5}
1,4-dioxane	1.5 lb.	1.2×10^{6}	6.3×10^{7}
	2.0 lb.	8.7×10^{5}	4.7×10^{7}
	5.0 lb.	2.9×10^{5}	1.6×10^{7}

TABLE 6
MARGINS OF SAFETY FOR EXPOSURE TO THE PUBLIC BY GROUND APPLICATION: DIETARY EXPOSURE

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	3.4×10^5	6.7×10^5
	2.0 lb.	2.5×10^5	4.9×10^5
	8.0 lb.	5.1×10^4	1.0×10^5
1,4-dioxane	1.5 lb.	8.0×10^5	4.3×10^7
	2.0 lb.	6.0×10^5	3.2×10^7
	5.0 lb.	2.0×10^5	1.1×10^7

TABLE 7
MARGINS OF SAFETY FOR EXPOSURE TO THE PUBLIC BY GROUND APPLICATION: FOREST GATHERERS

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	1.2×10^6	2.3×10^6
	2.0 lb.	9.0×10^5	1.8×10^6
	8.0 lb.	1.8×10^5	3.6×10^5
1,4-dioxane	1.5 lb.	2.8×10^6	1.5×10^8
	2.0 lb.	2.1×10^6	1.1×10^8
	5.0 lb.	6.9×10^5	3.7×10^7

TABLE 8
MARGINS OF SAFETY FOR EXPOSURE TO THE PUBLIC BY GROUND APPLICATION: CUMULATIVE EXPOSURE - INSIDE SPRAY AREA

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	3.2×10^5	6.5×10^5
	2.0 lb.	2.4×10^5	4.8×10^5
	8.0 lb.	4.5×10^4	9.0×10^4
1,4-dioxane	1.5 lb.	8.0×10^5	4.3×10^7
	2.0 lb.	6.0×10^5	3.2×10^7
	5.0 lb.	1.7×10^5	9.2×10^6

TABLE 9
MARGINS OF SAFETY FOR EXPOSURE TO THE PUBLIC BY GROUND APPLICATION: FOREST USERS (INHALATION + DERMAL EXPOSURE + DIETARY)

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	2.6×10^5	5.2×10^5
	2.0 lb.	2.0×10^5	4.0×10^5
	8.0 lb.	4.0×10^4	7.9×10^4
1,4-dioxane	1.5 lb.	6.4×10^5	3.4×10^7
	2.0 lb.	4.6×10^5	2.5×10^7
	5.0 lb.	1.5×10^5	8.2×10^6

TABLE 10
MARGINS OF SAFETY FOR EXPOSURE TO THE PUBLIC BY GROUND APPLICATION: MAXIMUM EXPOSED INDIVIDUAL (MEI)

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	2.5×10^5	5.1×10^5
	2.0 lb.	2.0×10^5	4.0×10^5
	8.0 lb.	3.5×10^4	7.1×10^4
1,4-dioxane	1.5 lb.	6.0×10^5	3.2×10^7
	2.0 lb.	4.6×10^5	2.5×10^7
	5.0 lb.	1.4×10^5	7.4×10^6

TABLE 11
MARGINS OF SAFETY FOR EXPOSURE TO PILOTS

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	2.4×10^5	4.7×10^5
	2.0 lb.	1.8×10^5	3.6×10^5
	8.0 lb.	4.0×10^3	7.9×10^3
1,4-dioxane	1.5 lb.	5.3×10^5	2.9×10^7
	2.0 lb.	4.4×10^5	2.3×10^7
	5.0 lb.	1.5×10^4	8.1×10^5

TABLE 12
MARGINS OF SAFETY FOR EXPOSURE TO MECHANICS

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	7.9×10^5	1.6×10^6
	2.0 lb.	5.8×10^5	1.2×10^6
	8.0 lb.	3.4×10^4	6.7×10^4
1,4-dioxane	1.5 lb.	1.9×10^6	1.0×10^8
	2.0 lb.	1.4×10^6	7.7×10^7
	5.0 lb.	1.3×10^5	6.8×10^6

TABLE 13
MARGINS OF SAFETY FOR EXPOSURE TO BATCHMEN

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	2.0×10^5	4.0×10^5
	2.0 lb.	1.5×10^5	3.0×10^5
	8.0 lb.	1.1×10^4	2.2×10^4
1,4-dioxane	1.5 lb.	4.6×10^5	2.5×10^7
	2.0 lb.	3.6×10^5	1.9×10^7
	5.0 lb.	4.0×10^4	2.2×10^6

TABLE 14
MARGINS OF SAFETY FOR EXPOSURE TO SUPERVISORS

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	2.8×10^6	5.7×10^6
	2.0 lb.	2.1×10^6	4.2×10^6
	8.0 lb.	1.8×10^5	3.6×10^5
1,4-dioxane	1.5 lb.	6.9×10^6	3.7×10^8
	2.0 lb.	5.1×10^6	2.7×10^8
	5.0 lb.	6.4×10^5	3.4×10^7

TABLE 15
MARGINS OF SAFETY FOR EXPOSURE TO OBSERVERS

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	1.1×10^{7}	2.2×10^{7}
	2.0 lb.	8.2×10^{6}	1.6×10^{7}
	8.0 lb.	3.7×10^{5}	7.5×10^{5}
1,4-dioxane	1.5 lb.	2.7×10^{7}	1.5×10^{9}
	2.0 lb.	2.0×10^{7}	1.1×10^{9}
	5.0 lb.	1.4×10^{6}	7.7×10^{7}

TABLE 16
MARGINS OF SAFETY FOR EXPOSURE TO BACKPACK WORKERS

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	5.8×10^{4}	1.2×10^{5}
	2.0 lb.	4.4×10^{4}	8.8×10^{4}
	8.0 lb.	4.4×10^{3}	8.8×10^{3}
1,4-dioxane	1.5 lb.	1.4×10^{5}	7.4×10^{6}
	2.0 lb.	1.0×10^{5}	5.6×10^{6}
	5.0 lb.	1.7×10^{4}	9.1×10^{5}

Table 17
MARGIN OF SAFETY FOR EXPOSURE TO MIXER/LOADER
(mechanical application)

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	2.7×10^{5}	5.4×10^{5}
	2.0 lb.	2.0×10^{5}	4.0×10^{5}
	8.0 lb.	3.0×10^{3}	5.8×10^{3}
1,4-dioxane	1.5 lb.	6.0×10^{5}	3.2×10^{7}
	2.0 lb.	4.6×10^{5}	2.5×10^{7}
	5.0 lb.	1.0×10^{4}	5.4×10^{5}

Table 18
MARGIN OF SAFETY FOR EXPOSURE TO APPLICATOR
(mechanical equipment)

Impurity	Herbicide A.I. Application Rate/Ac.	Systemic MOS	Reproductive MOS
2-butoxyethanol	1.5 lb.	6.4×10^5	1.3×10^6
	2.0 lb.	4.7×10^5	9.4×10^5
	8.0 lb.	3.0×10^3	5.9×10^3
1,4-dioxane	1.5 lb.	1.5×10^6	7.8×10^7
	2.0 lb.	1.1×10^6	5.9×10^7
	5.0 lb.	1.0×10^4	5.5×10^5

TOXICITY TO FISH

For aquatic organisms, chemicals with LC_{50} values greater than 10 ppm are considered only slightly toxic (Clarke et al. 1970). In laboratory aquarium studies, Dawson et al. (1977) reported 96-hour, LC_{50} values for EGBE of 1,490 ppm for bluegill sunfish (a freshwater species) and 1,250 ppm for the tidewater silverside (a saltwater species). They also reported LC_{50} values for dioxane of >10,000 ppm for the bluegill and 6,700 ppm for the silverside. These data suggest that both chemicals are, at most, only slightly toxic to fish.

Actual fish mortality rates depend on the concentration of the chemicals in the water and the length of time exposure occurs. Estimated concentrations of these impurities in water as a result of herbicide applications were calculated by multiplying the herbicide dose to fish for the 1 lb./acre application rate (see FEIS, page F-84) by the expected herbicide application rates and by the correction factor for the impurity. The estimated environmental concentrations are shown in Table 19.

EPA (1986) criteria were used to estimate the risk to aquatic species from exposures to these concentrations of impurities (see FEIS, page 4-48). According to EPA, if the ratio (Q-value) of the estimated environmental concentration (EEC) to the LC_{50} (Q-value = EEC/LC_{50}) is less than 0.1, there is no acute toxicity. Comparing the estimated concentrations of the impurities in water with LC_{50} values for freshwater and saltwater species gives extremely low Q-values (Table 19) even for worst case concentrations. Based on these comparisons, there is little risk of acute toxic effects to aquatic species. The amounts of these impurities are so low in the herbicide formulations that they present almost no risk to fish or other aquatic organisms.

Table 19
COMPARISON OF ESTIMATED IMPURITY CONCENTRATIONS IN WATER AND FISH TOXICITY VALUES
(PPM)

Impurity	Herb. A.I. Applica. Rate/Ac.	Estimated Environ. Concen..	LC_{50} Blue-gill	LC_{50} Silver-side	Q-Value Bluegill	Q-Value Silverside
EGBE	1.5 lb.	7.3×10^{-5}	1,490	1,250	4.9×10^{-8}	5.8×10^{-8}
	2.0 lb.	9.7×10^{-5}	1,490	1,250	6.5×10^{-8}	7.8×10^{-8}
	8.0 lb.	3.9×10^{-4}	1,490	1,250	2.6×10^{-7}	3.1×10^{-7}
Dioxane	1.5 lb.	1.5×10^{-5}	>10,000	6.700	1.5×10^{-9}	2.2×10^{-9}
	2.0 lb.	2.0×10^{-5}	>10,000	6,700	2.0×10^{-9}	3.0×10^{-9}
	5.0 lb.	4.9×10^{-5}	>10,000	6,700	4.9×10^{-9}	7.3×10^{-9}

Using an acute oral LD_{50} of 470 mg/Kg (Dow 1990), EGBE is classified as moderately toxic (EPA category II). Dioxane is classified as slightly toxic (EPA category III) with an acute oral LD_{50} of 4200 mg/Kg (Layton et al. 1987, Lewis and Sweet 1984).

Doses of the impurities were calculated for deer and rabbits by multiplying the estimated doses for a 1 lb./acre application of herbicide (FEIS, Appendix F, page F-85) by the actual herbicide application rates and by the correction factor for the impurity (Table 20). The dermal and oral doses were combined for this analysis on the worst case assumption that animals are sprayed and also feed on treated vegetation.

According to the EPA criteria, doses lower than 1/5 LD_{50} are assumed to pose low risk to animals. None of the impurity doses exceed the 1/5 LD_{50} criteria recommended by EPA (1986) for assessing risk to animals. In fact, none of the doses exceed 1/1000 of the lowest LD_{50} (220 mg/Kg). Therefore, these impurities present little or no hazard to wildlife populations, even under worst case circumstances.

Doses to quail and ducks were also calculated following procedures outlined in the FEIS (page 4-43). No data were found in the literature on the toxicity of these chemicals to birds. Therefore, no direct comparison with LD_{50} values is possible. Based on general comparisons of the relative sensitivity of birds and mammals to various chemicals, we conclude that the extremely low doses of these ingredients pose a low risk to birds.

Table 20
WILDLIFE DOSES (mg/Kg)

Impurity	Herb. A.I. Applica. Rate/Ac.	Dose to Deer mg/kg	Dose to Rabbit mg/kg	Dose to Quail mg/kg	Dose to Duck mg/kg	Oral[a] LD_{50} mg/kg	Dermal[b] LD_{50} mg/kg
EGBE	1.5 lb.	0.013	0.031	0.0063	0.012	470	220
	2.0 lb.	0.017	0.041	0.0083	0.016	470	220
	8.0 lb.	0.070	0.16	0.033	0.065	470	220
Dioxane	1.5 lb.	0.0026	0.0062	0.0013	0.0025	4200	-
	2.0 lb.	0.0035	0.0083	0.0017	0.0033	4200	-
	5.0 lb.	0.0088	0.021	0.0042	0.0082	4200	-

a Based on rat (Dow Chemical Company 1990a, Layton et al. 1987, Lewis and Sweet 1984)
b Based on rabbit (Dow Chemical Company 1990a)

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APPENDIX

CANCER RISK ASSESSMENT FOR FORESTRY APPLICATIONS OF HERBICIDE SURFACTANT CONTAINING 1,4-DIOXANE

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INTRODUCTION

1,4-Dioxane is a manufacturing by-product contained in ethoxylated surfactants. Some of these surfactants are commonly used as adjuvants in herbicide formulations developed for forestry use. 1,4-Dioxane has been shown to produce tumors in laboratory animals at high dose levels. This risk assessment document outlines the basis for Monsanto's conclusion that these formulations can be used with no significant risk to human health.

Risk assessment is a process whereby an evaluation is made of the potential adverse human health effects that may result from chemical exposure. In the case of 1,4-dioxane, where the health effect of concern is cancer, an attempt is made to quantify the probability of an exposed individual developing cancer based on the results of animal studies.

Currently in the North American population, the probability (i.e. risk) of contracting cancer spontaneously is approximately 30%. This risk assessment was performed to estimate the "excess lifetime risk" of developing cancer. This term specifically refers to the theoretical increase in cancer risk above the spontaneous background rate which results from lifetime exposure to 1,4-dioxane.

The basic components of this risk assessment include: 1) a hazard evaluation which examines the data describing the agent's ability to produce carcinogenic effects; 2) a dose-response assessment to define the relationship between exposure and potential response (cancer incidence in this case) in the region of human exposure; 3) an exposure assessment to define the range of probable human exposures to the chemical; and 4) the risk characterization to quantify the hypothetical probability of exposed individuals or populations developing the health effect of concern.

HAZARD ASSESSMENT

The results of toxicology tests performed in animals indicate that 1,4-dioxane may pose a possible human cancer risk. This conclusion is based on the presence of benign and malignant tumors in different species of animals tested. Because comprehensive reviews of these tests are readily available, the relevant results will be only briefly summarized here.

Oncogenicity studies in animals

Nasal and liver tumors were reported in rats ingesting high concentrations (7000-18,000 ppm) of dioxane in drinking water for 14 to 23 months. Liver and gall bladder tumors have been produced in guinea pigs given drinking water containing dioxane for 23 months. As in the previous studies, the concentrations were high (5,000 - 20,000 ppm) relative to human exposure. In studies conducted for the National Cancer Institute (NCI), liver tumors were found in rats only. No increase in the incidence of tumors was observed in rats following 1,4-dioxane inhalation.

Genetoxicity studies

1,4-Dioxane induced DNA strand breaks in rat hepatocytes in vitro. It did not induce sex-linked recessive lethal mutations in Drosphila or aneuploidy in yeast. It induced chromosomal alterations in plants but was not mutagenic to bacteria.

Overall evaluation

A weight-of-evidence evaluation for 1.4-dioxane indicates that there is sufficient evidence of carcinogenicity in animals. According to guidelines used by the International Agency for Research on Cancer (IARC), 1.4-dionxane meets the criteria for group 2B.

DOSE-RESPONSE ASSESSMENT

The current U.S. regulatory policy for assessing excess human cancer risk is based on the assumption that dose response thresholds cannot be demonstrated for oncogenic effects. In other words, some finite level of risk is assumed to be present no matter how low the exposure. Therefore, mathematical probability models are used to provide an estimate of theoretical human cancer risk associated with environmental exposure to chemical producing oncogenic responses in laboratory animals. A number of models are available for extrapolating tumor risk observed at high experimental doses to the much lower expected human doses.

Selection of extrapolation model

Since the mechanism (s) for oncogenicity are unknown for most chemicals, there is little scientific basis for selection of one extrapolation model over another. When relevant data or biological evidence of the mechanism of oncogenicity are limited or do not exist, U.S. regulatory agencies (including

the EPA) prefer to use the very conservative linearized multistage model. Other models have been developed and are considered to yield more realistic estimates of risk. Nevertheless, to be consistent with current U.S. regulatory practice, the conservative linearized multistage model is used in this risk assessment.

Selection of tumor data set

The U.S. Food and Drug Administration and the National Cancer Institute have used quantitative risk assessment (linearized multistage procedure) to estimate the upper-bound level of excess lifetime human risk from exposure to this chemical. This assessment was done using the dose-response data from the most sensitive site and species, which was determined to be squamous cell carcinomas of the nasal turbinates in male rats. Dosage and tumor response data from this study are shown below.

Dose (mg/kg/day)		
	Human	Tumor
Administered	Equivalent	Incidence
0	0	0/33
240	61	12/33
530	135	16/34

Interspecies dosage scaling

The human equivalent doses listed above were determined from the actual doses administered to the laboratory animals using interspecies dosage scaling. The goal of interspecies dosage scaling is to correct for differences in metabolicrate which may affect the concentration at the target site. Dosages producing similar effects in multiple species and comparative metabolism data are examples of kinds of information which, if available, can be utilized in the determination of the appropriate scaling factor.

In the absence of compound-specific toxicological, metabolic, and pharmacokinetic data, the U.S. EPA has taken the conservative approach of scaling between species on the basis of surface area. In contrast, other scientists and organizations (Crump et al., U.S. Food and Drug Administration, Food Safety Council, California Department of Food and Agriculture) have concluded that scaling between species based on body weight is more appropriate.

The rationale given for scaling based on body weight is as follows. Several physiological indices, including basal oxygen consumption, activity of many liver enzymes, inulin and urea clearance, and nitrogen output are closely related to the 3/4 power of body weight (Davidson et al., 1986). Since

mechanisms of biotransformation and elimination of xenobiotics may be related to basal metabolism and hepatic and renal function, body weight to the 3/4 power is used when a generic scaling factor is needed.

In this risk assessment, the Human Equivalent Doses, based on body weight to the 3/4 power, were obtained by multiplying the animal doses by 0.254 (California Department of Food and Agriculture, 1987).

Linearized Multistage Model Potency Estimate

The Q1* or potency was determined to be 7.6×10^{-3} $(mg/kg/day)^{-1}$

EXPOSURE ASSESSMENT

Introduction

Exposures to forestry workers have been estimated in environmental impact statements (EIS) prepared for the United States Department of Agriculture Forest Service (1988,1989). In these documents, exposure assessments were conducted for various workers involved in aerial, mechanical ground, and manual ground operations. Calculated exposures were highest for aerial mixer/loaders and backpack sprayers. Therefore, dioxane doses are calculated only for these workers. Exposures to other worker will be lower and are not considered here.

Calculations of Exposure and Dose for Different Scenarios

The absorbed dose of 1,4-dioxane is calculated for each scenario (mixer/loader and backpack applicator) using the following equation:

DOSE = FDOSE X DCF DPCF X RATE X AREA

where:

FDOSE = dose from field study with 2,4-D (mixer/loader) or glyphosate (backpack) reported below

DCF = the 1,4-dioxane correction factor based on the ration of dioxane to a.i. in ROUNDUP herbicide

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DPCF = the dermal penetration correction factor derived from the ration of the dermal penetration of 1,4-dioxane (assumed to be 10% as explained in text to the dermal penetration of 2,4-D (6%; for mixer/loader calculations) or glyphosate (2%; for backpack applicator calculations)

AREA = the number of acres treated in 1 day

RATE = the application rate for ROUNDUP herbicide

The lifetime average daily dose (LADD) is then determined from the yearly absorbed dose. Individual calculations are shown below.

A. DOSE CALCULATIONS

Dose - Field Study Data
Aerial mixer/loader

Estimates or exposure were obtained from the U.S. Forest Service EIS prepared for the Pacific Northwest Region. In the EIS, exposure data was obtained from field worker exposure studies conducted with 2,4-D by Lavy et al. (1982, 1984), Nash et al. (1982), and Franklin et al. (1982).

Levy et al. (1982) monitored three helicopter spray crews for worker exposure to 2,4-D on two separate dates: the first observing normal precautions, the second using special protective clothing and procedures. Nash et al. (1982) studied worker exposure to 2,4-D during aerial spraying in Washington and ground spraying in North Dakota under normal conditions without special precautions. Lavy et al. (1984) investigated herbicide exposure to four spray crews (20 workers in each crew) by monitoring urine levels over two 5-day periods. Franklin et al. (1982) estimated worker exposure in pasture brush clearing operations in Saskatchewan.

Based on these studies, the absorbed dose of 2,4-D for a routine-realistic aerial application was given as 0.000108 mg/kg/lb a.i. applied. It should be noted that in the EIS analysis inhalation doses were not estimated separately for workers; they were included with dermal doses in the estimated total worker doses based on herbicide levels in the urine of workers in the field experiments. This was done because a variety of studies have shown that inhalation exposure is very small compared with dermal exposure (Draper and Street, 1982); Nigg and Stamper, 1983; Libich et al., 1984).

Backpack applicator

A forestry worker exposure study was recently completed by the Georgia Tech Research Institute. This was a biological monitoring study employing 16 workers; these workers wore long pants, long-sleeved shirts but no gloves. Analytical samples were analyzed for the Institute by Monsanto. This study yields better estimates of exposure that the EIS analysis because it was actually conducted with glyphosate (not 2,4-D) and used a current protocol with improved quality control procedures. The exposure value obtained from the Georgia Tech study was 0.000294 mg/kg/lb a.i. applied.

Corrections for dioxane ratio and penetration

The absorbed dose of herbicide was given as 0.000108 mg/kg/lb a.i. applied for mixer/loaders and 0.000294 mg/kg/lb a.i. applied for backpack sprayers. To determine the absorbed dose of 1,4-dioxane, corrections must be made for (a) the concentration of dioxane in ROUNDUP and (b) differences in the dermal penetration between the contaminant and the herbicide.

The concentration of glyphosate in the formulated product is 30.4% and the concentration of 1,4-dioxane is assumed to be 0.03%. This is based on extensive analyses (n=40) conducted on retained product samples located at various Monsanto manufacturing and research technology locations. The results of these analyses showed that the mean 1,4-dioxane, concentration was was 160$\pm$ 56 ppm with a range of 56 to 307 ppm. thus, a reasonable estimate of the upper-limit concentration of 1,4-dioxane contained in the herbicide formulation is 300 ppm or 0.03%. It is assumed that the deposition and inhalation of 1,4-dioxane is proportional to its concentration in the formulation.

Monsanto now requires that the surfactant contain no more than 150 ppm 1,4-dioxane. since the surfactant concentration is 15% in the formulated product, the herbicide concentrate will contain no more than 23 ppm 1,4-dioxane. Subsequent calculations of exposure and risk based on the current 23 ppm 1,4-dioxane level are not presented here but are summarized in Table 2.

The systemic absorption 1,4-dioxane from dermal exposure (24 hours) has been estimated in monkeys (Marzulli and Maiback, 1981). Dermal penetration was shown to be 2.3 $\pm$ 0.2% and 3.4 $\pm$ 1.2% using methanol and skin lotion, respectively, as vehicles. A conservative assumption for human dermal penetration would be 10%. This value will be used in subsequent calculations even though the data indicates that the actual penetration of 1,4-dioxane is somewhat lower.

The dermal penetration is approximately 2% for glyphosate (Monsanto, unpublished data) and is assumed to be 6% for 2,4-D (U.S. Department of Agriculture, 1988).

Therefore, the absorbed dioxane dose for the mixer/loader is:

FSDOSE X CDF X DPCF

or

$$\frac{0.000108 \text{ mg}}{\text{kg-lb a.i. applied}} \times \frac{0.03\% \text{ dioxane}}{30.4\% \text{ a.i.}} \times \frac{10\%}{6\%}$$

$= 1/78 \times 10^{-7}$ mg/kg/lb a.i. applied

For the backpack applicator, the absorbed dioxane dose is:

$$\frac{0.000294}{\text{kg-lb a.i. applied}} \times \frac{0.03\% \text{ dioxane}}{30.4\% \text{ a.i.}} \times \frac{10\%}{2\%}$$

$= 1.45 \times 10^{-6}$ mg/kg/lb a.i. applied

Rate

It is assumed that glyphosate will be typically sprayed at or below the rates (routine-realistic) listed in the Forestry EIS for the Pacific Northwest Region. These rates are:

	lb a.i. / acre
Aerial Mixer/Loader	2.0
Backpack Applicator	1.5

Area

The maximum area that would be aerially-sprayed in one day is considered to be approximately 300 acres. For backpack applicator, the maximum area that can be sprayed in one day is approximately 3.5 acres, even in flat terrain. Very few applicators could spray more than 2.5 acres a day. This is particularly true because the terrain is generally uneven and difficult to work on.

The typical anticipated number of days/year that a worker applies the product is listed in the Forestry EIS (Southern Region) as:

Aerial mixer/loader:	2
Manual ground backpack sprayer:	13

However, the estimate for the aerial mixer/loader is considered to be low. An aerial crew may spray up to 52 times during the year; this includes 4-5 applications/week for 2 months in the fall (conifer release) and 2-3

applications/week for 4 weeks in the spring or early summer (site preparation).

Therefore, typical dioxane exposure during the year for the aerial mixer/loader is:

$$\frac{1.78 \times 10^{-7} \text{ mg}}{\text{kg-lb a.i. applied}} \times \frac{2 \text{ lb a.i.}}{\text{acre}} \times \frac{300 \text{ acres}}{\text{day}} \times \frac{52 \text{ days}}{\text{yr}}$$

$$= 5.6 \times 10^{-3} \text{ mg/kg/yr}$$

Dioxane exposure for the backpack applicator during the year is:

$$\frac{1.45 \times 10^{-6}}{\text{kg-lb a.i. applied}} \times \frac{1.5 \text{ lb a.i.}}{\text{acre}} \quad \frac{3.5 \text{ acres}}{\text{day}} \quad \frac{13 \text{ days}}{\text{yr}}$$

$$= 9.9 \times 10^{-5} \text{ mg/kg/yr}$$

B. Lifetime average daily dose (LADD):

For this risk assessment, the cumulative annual systemic dose is expressed as an average daily exposure prorated over a lifetime. When expressed as a lifetime average daily dose (LADD), human exposure can be compared to exposures received by animals developing tumors in the chronic study. In the calculations of an LADD, 35 years of product use and 70-year life expectancy are assumed. The LADD is calculated as follows:

$$\text{LADD} = \frac{\text{mg dioxane/kg/yr} \times 35 \text{ yr}}{365 \text{ days/yr} \times 70 \text{ yr}}$$

$= (5.6 \times 10^{-3})\ (35)/(365)\ (70) \quad = 7.6 \times 10^{-6}$ Aerial mixer/loader

$= (9.9 \times 10^{-5})\ (35)/(365)\ (70) \quad = 1.4 \times 10^{-7}$ Backpack applicator

RISK CHARACTERIZATION

From the LADD exposure estimates, it is possible to predict added human cancer risk for the various exposure scenarios. Risk is determined by the following equation:

$$\text{Risk}_{\text{UCL 95}} = \text{Exposure (mg/kg/day)} \times \text{Potency (mg.kg.day)}^{-1}$$

This value is the 95% upper confidence limit on risk calculated with the very conservative linearized multistage model. This means that there is 95% probability that the true risk will be lower than the calculated value. Also, the risks were calculated using estimates of exposure and absorbed dose that were based on a number of conservative assumptions. Thus the true estimate of risk to workers is expected to be lower than the values reported here.

Estimated risks for forestry workers are presented in Tables 1 and 2. The larger risks were calculated for the aerial mixer/loader (approximately 6×10^{-8} and 4×10^{-9} at 300 and 23 ppm dioxane, respectively), while the backpack applicator has the smaller risk (approximately 1×10^{-9} and 8×10^{-11} at 300 and 23 ppm, respectively).

Again, it must be pointed out that these risk estimates were calculated for workers having the highest potential for exposure. Risks to other groups of workers performing different operations would be lower.

The U.S. Environmental Protection Agency and Food and Drug Administration routinely consider cancer risks of less than 1×10^{-6} (one in one million) to be negligible. In fact, the FDA approves materials contaminated with 1,4-dioxane as indirect food additives when the calculated risks are below this level. Conservative estimates of risk resulting from herbicide use are much lower than 1×10^{-6} even for workers with the highest potential for exposure. Therefore, this analysis indicates that the carcinogenic risk from exposure to 1,4-dioxane in glyphosate herbicide formulations is negligible for occupationally exposed individuals.

Table 1. Risks for Forestry Workers Based on 300 ppm 1,4-Dioxane in Herbicide

	Aerial Mixer/Loader	Manual Ground Backpack
Glyphosate Dose (mg/kg/ lb a.i. applied	0.000108	0.000294
Dioxane in Formulation (ppm)	300	300
Application Rate lb/acre	2.0	1.5
Area/Project or Day Acres	300	3.5
Applications/Yr	52	13
Dioxane Dose (mg/kg/yr)	5.6×10^{-3}	9.9×10^{-5}
LADD	7.6×10^{-6}	1.4×10^{-7}
Q_1^*	7.6×10^{-3}	7.6×10^{-3}
RISK	5.8×10^{-8}	1.1×10^{-9}

TABLE 2. Risks for Forestry Workers Based on 23 ppm, 1.4-Dioxane in Herbicide

	Aerial Mixer/Loader	Manual Ground Backpack
Glyphosate Dose (mg/kg/ lb a.i. applied	0.000108	0,000294
Dioxane in Formulation (ppm)	23	23
Application Rate lb/acre	2.0	1.5
Area/Project or Day Acres	300	3.5
Applications/Yr	52	13
Dioxane Dose (mg/kg/yr)	4.2×10^{-4}	7.6×10^{-6}
LADD	5.8×10^{-7}	1.0×10^{-8}
Q_1^*	7.6×10^{-3}	7.6×10^{-3}
RISK	4.4×10^{-9}	7.6×10^{-11}

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